DORMOSEDAN GEL®
detomidine hydrochloride 7.6 mg/ml oromucosal gel

EXCEDE®
(Ceftiofur Crystalline Free Acid)
Sterile Suspension

TWO TREATMENTS. ONE SOLUTION FOR YOUR SICK HORSE.

Many people find administering antibiotics difficult and time-consuming. For a full course of therapy, your horse must receive the full dose, at regular intervals as prescribed by a veterinarian. This can disrupt schedules and cause added stress for your horse and you, especially if your horse doesn't appreciate oral antibiotics.

EXCEDE® WORKS IN JUST TWO DOSES.

EXCEDE® (Ceftiofur Crystalline Free Acid) Sterile Suspension

- EXCEDE (*ceftiofur crystalline free acid*) Sterile Suspension is the first and only licensed antibiotic for horses that offers a full 10-day course of therapy in just two treatments.
- By moving away from treating once or twice daily with traditional oral or injectable antibiotics, the two-treatment regimen of EXCEDE makes the process less stressful for the horse and offers added control over treatment compliance as well as convenience for the administering horse owner or veterinarian.
- EXCEDE is for the treatment of lower respiratory tract infections in horses caused by *Streptococcus equi* subspecies *zooepidemicus* (*S. zooepidemicus*).
- Ask your veterinarian if EXCEDE is right for your horse.

IMPORTANT SAFETY INFORMATION:

The use of EXCEDE is contraindicated in animals with known allergy to ceftiofur or to the ß-lactam group (penicillins and cephalosporins) of antimicrobials. Do not use EXCEDE in horses intended for human consumption. The administration of antimicrobials in horses under conditions of stress may be associated with diarrhea, which may require appropriate veterinary therapy. Though safe in cattle when properly administered, inadvertent intra-arterial injection is possible and fatal. EXCEDE has a pre-slaughter withdrawal time of 13 days in cattle. Do not use in calves to be processed for veal. For complete details, refer to the full prescribing information, or visit **www.Excede.com.**

LESS STRESS FOR YOUR HORSE, AND SAFETY FOR YOU.

Even the most gentle of horses can become nervous or unruly when facing common yet stressful husbandry procedures, like:

- Shoeing/trimming
- Bandage changing
- Sheath cleaning
- Body clipping
- Bridle path trimming
- Mane pulling
- First-time turnouts for fractious horses

DORMOSEDAN GEL® IS A SAFE AND EFFECTIVE MILD, STANDING SEDATIVE ADMINISTERED BY YOU.

- Easy-to-use option for needle-shy horses and for horse owners who are uncomfortable giving an injection
- Available in single-dose, needleless syringes — administered under your horse's tongue
- Prescribed by a veterinarian and administered by you — this FDA-approved oral gel formulation can be obtained only through a veterinary prescription
- To learn more, go to DormosedanGel.com

DORMOSEDAN GEL®
detomidine hydrochloride 7.6 mg/ml oromucosal gel

IMPORTANT SAFETY INFORMATION:
DORMOSEDAN GEL is contraindicated in horses with known hypersensitivity to detomidine. Intravenous potentiated sulfonamides should not be used in anesthetized or sedated horses, as potentially fatal dysrhythmias may occur. Do not use DORMOSEDAN GEL in horses with pre-existing atrioventricular (AV) or sinoatrial (SA) blocks, cardiovascular disease, respiratory disorders, liver or kidney diseases, or in conditions of shock, severe debilitation or stress due to extreme heat, cold, fatigue or high altitude. Appropriate precautions should be taken while handling and using gel-dosing syringes, as DORMOSEDAN GEL can be absorbed following direct exposure to skin, eyes or mouth, and may cause irritation. The use of impermeable gloves is advised. Please see the full prescribing information, or go to **www.DormosedanGel.com.**

NADA #141-306, Approved by FDA

DORMOSEDAN GEL®

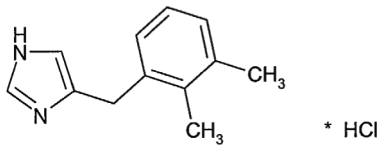
(detomidine hydrochloride)
Alpha$_2$-agonist oromucosal gel
Rx only
For Sedation and Restraint in Horses Only

CAUTION:

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

DORMOSEDAN (detomidine hydrochloride) GEL is a synthetic alpha$_2$-adrenoreceptor agonist with sedative properties. Each mL of DORMOSEDAN GEL contains 7.6 mg detomidine hydrochloride. The chemical name is 1H imidazole, 4-[(2,3-dimethylphenyl) methyl]-hydrochloride. Detomidine hydrochloride is a white, crystalline, water-soluble substance having a molecular weight of 222.7. The molecular formula is $C_{12}H_{14}N_2$•HCl and the structural formula is



INDICATIONS:

DORMOSEDAN GEL is indicated for sedation and restraint in horses.

DOSAGE AND ADMINISTRATION:

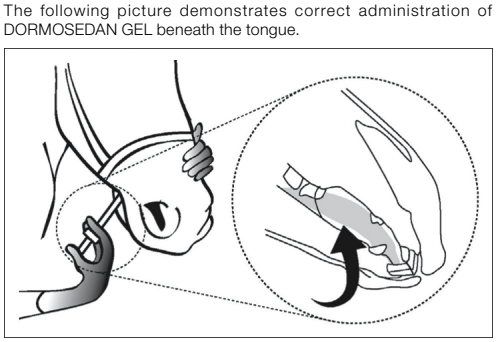
DORMOSEDAN GEL produces sedation when administered sublingually at 0.018 mg/lb (0.040 mg/kg). DORMOSEDAN GEL must be placed beneath the tongue of the horse and is not meant to be swallowed. The dosing syringe delivers the product in 0.25 mL increments. The following dosing table may be used to determine the correct dose of DORMOSEDAN GEL (Table 1).

Table 1: Sublingual dosing of DORMOSEDAN GEL

Approximate body weight (lb)	Range of doses (mg/lb)	Approximate body weight (kg)	Range of doses (mg/kg)	Dose volume (mL)
330–439	0.023–0.017	150–199	0.051–0.038	1.00
440–549	0.022–0.017	200–249	0.047–0-038	1.25
550–659	0.021–0.017	250–299	0.046–0.038	1.50
660–769	0.020–0.017	300–349	0.044–0.038	1.75
770–879	0.019–0.017	350–399	0.043–0.038	2.00
880–989	0.019–0.017	400–449	0.043–0.038	2.25
990–1099	0.019–0.017	450–499	0.042–0.038	2.50
1100–1209	0.019–0.017	500–549	0.042–0.038	2.75
1210–1320	0.019–0.017	550–600	0.041–0.038	3.00

Use impermeable gloves when handling the product. Remove the syringe from the outer carton. While holding the plunger, turn the ring-stop on the plunger until the ring is able to slide freely up and down the plunger. Position the ring in such a way that the side nearest the barrel is at the desired volume marking. Turn the ring to secure it in place. Make sure that the horse's mouth contains no feed. Remove the cap from the tip of the syringe and save for cap replacement. Insert the syringe tip into the horse's mouth from the side of the mouth, placing the syringe tip beneath the tongue at the level of the commissure of the mouth. Depress the plunger until the ring-stop contacts the barrel, depositing the product beneath the tongue.

The following picture demonstrates correct administration of DORMOSEDAN GEL beneath the tongue.



Take the syringe out of the horse's mouth, recap the syringe and return it to the outer carton for disposal. Remove gloves for disposal.

For the best results, allow adequate time (a minimum of 40 minutes) between administration of DORMOSEDAN GEL and beginning the procedure. In general, horses show sedative effects lasting approximately 90–180 minutes.

Withhold food and water until the sedative effects of the product wear off.

CONTRAINDICATIONS:

DORMOSEDAN GEL is contraindicated in horses with known hypersensitivity to detomidine. Intravenous potentiated sulfonamides should not be used in anesthetized or sedated horses as potentially fatal dysrhythmias may occur.

Do not use DORMOSEDAN GEL in horses with pre-existing atrioventricular (AV) or sinoatrial (SA) blocks, respiratory disease, or chronic renal failure.

WARNINGS:

For sublingual use in horses only. Do not use in horses intended for human consumption.

HUMAN WARNINGS: Not for human use. Keep out of the reach of children. **Use impermeable gloves during drug administration and during procedures that require contact with the horse's mouth.** Following sublingual administration of detomidine oromucosal gel, drug concentrations up to 0.072 mg/mL were measured at 30 minutes post dose in equine saliva, equivalent to less than 1% of the original detomidine concentration in the gel. Mean drug concentrations fall to less than 0.010 mg/mL by 2 hours after drug administration, after which a slow decline occurs for several additional hours.

DORMOSEDAN GEL can be absorbed following direct exposure to skin, eyes or mouth, and may cause irritation. Skin and mucosal contact with the product should be avoided. Use impermeable gloves at all times.

In case of accidental eye exposure, rinse abundantly with fresh water. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing.

Appropriate precautions should be taken while handling and using gel syringes. Accidental exposure could cause adverse reactions, including sedation, hypotension and bradycardia. Seek medical attention immediately but do not drive because sedation or changes in blood pressure may occur.

Individuals with cardiovascular disease (for example, hypertension or ischemic heart disease) should take special precautions to avoid exposure to this product.

Caution should be exercised when handling sedated horses. Handling or any other sudden stimuli, including noise, may cause a defense reaction in an animal that appears to be heavily sedated.

Rare cases of human abuse of detomidine products have been reported. DORMOSEDAN GEL should be managed to prevent the risk of diversion, through such measures as restriction of access and the use of drug accountability procedures appropriate to the clinical setting.

The material safety data sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users or to obtain a copy of the MSDS for this product call 1-800-366-5288.

Note to physician: This product contains an alpha$_2$-adrenoceptor agonist.

PRECAUTIONS:

DORMOSEDAN GEL must be placed beneath the tongue of the horse. Unlike most oral veterinary products, this product is not meant to be swallowed. Swallowing could result in ineffectiveness.

DORMOSEDAN GEL does not provide analgesia. Do not use for painful procedures.

Do not use with other sedative drugs because the effects may be additive.

Repeat dosing has not been evaluated.

The use of an alpha$_2$-agonist reversal agent with DORMOSEDAN GEL has not been evaluated.

Before initiating any procedure, allow sedation to fully develop. Nervous or excited horses with high levels of endogenous catecholamines may exhibit a reduced pharmacological response to alpha$_2$-adrenoceptor agonists like detomidine. In agitated horses, the onset of sedative effects could be slowed, or the depth and duration of effects could be diminished or nonexistent. When the product is administered, the animal should be allowed to rest in a quiet place for a minimum of 40 minutes.

Do not use DORMOSEDAN GEL in horses with cardiovascular disease, respiratory disorders, liver or kidney diseases, or in conditions of shock, severe debilitation or stress due to extreme heat, cold, fatigue or high altitude. Protect treated horses from temperature extremes. As with all alpha$_2$-adrenoceptor agonists, the potential for isolated cases of hypersensitivity, including paradoxical response (excitation), exists.

DORMOSEDAN GEL has not been evaluated in ponies, miniature horses, or horses younger than one year of age.

DORMOSEDAN GEL has not been evaluated for use in breeding, pregnant, or lactating horses.

ADVERSE REACTIONS:

Clinical field study:

In a U.S. field study of 270 horses sedated to facilitate completion of various veterinary and husbandry procedures, the following adverse reactions were reported in 202 horses treated with DORMOSEDAN GEL and 68 horses treated with placebo:

Table 2: Adverse reactions (number of horses) during the clinical field study

Clinical Sign	DORMOSEDAN GEL N = 202	Placebo N = 68
Sweating	20	0
Penile relaxation	12	0
Bradycardia (≤ 20 bpm)	11	0
Second degree AV block	9	0
Frequent urination	9	0
Piloerection	4	0
Marked ataxia	3	0
Facial/oral edema	3	0
Hypersalivation	2	0
Nasal discharge	2	0
Flatulence	1	0
Muscle tremors	1	1
Epiphora	1	0
Pale mucous membranes	1	0
Swollen sheath	1	0

In a laboratory study, transient erythema of the mucous membranes was seen in 2 (of 8) horses that received the recommended dose of detomidine gel.

Mild ataxia (horse stable but swaying slightly) was observed in 54% of DORMOSEDAN GEL-treated horses and in 4% of the placebo-treated horses at 40 minutes post treatment administration. Moderate ataxia was observed in 25% of DORMOSEDAN GEL-treated horses (0% placebo) at 40 minutes post treatment. Moderate to marked ataxia continued to 90 minutes for 5% and to 120 minutes for 4% of DORMOSEDAN GEL-treated horses.

CLINICAL PHARMACOLOGY:

Detomidine is a potent non-narcotic alpha$_2$-adrenoceptor agonist which produces sedation with a central effect inhibiting the transmission of noradrenalin-mediated nervous impulses. Blood pressure is initially increased due to peripheral vasoconstriction, subsequently dropping to normal or slightly below normal levels. Vasoconstriction may cause mucous membranes to appear pale or mildly cyanotic. This initial vasopressor response is accompanied by a compensatory marked decrease in heart rate mediated by a vagal baroreceptor. The peripheral pulse may feel weak and a transient change in the conductivity of the cardiac muscle may occur, as evidenced by first and second degree atrioventricular blocks. Other arrhythmias may occur. Detomidine also decreases the respiratory rate and decreases body temperature. Detomidine causes depression of gastrointestinal motility due to decrease in smooth muscle activity, increases blood glucose levels due to inhibition of insulin release, and increases production of urine 2 to 4 hours after treatment. In some horses, sweating, salivation and slight muscle tremors may be seen. Partial, transient penis prolapse may occur in stallions and geldings. Because of continued lowering of the head during sedation, mucus discharges from the nose with occasional swelling of the head, particularly around the eyes, may be seen.

Detomidine is oxidized mainly in the liver. Most metabolites are excreted in the urine. Halflife (T½) is 1–2 hours. Detomidine is rapidly distributed; volume of distribution (Vd) varies between 0.69 L/kg and 1.89 L/kg. Protein binding is about 85%.

Detomidine is a high extraction ratio drug. Alterations in liver blood flow (the site of detomidine metabolism) can change the rate of drug clearance and, consequently, drug exposure. The sedative effects of detomidine (using head droop as a marker for sedation) are highly correlated to blood concentration, regardless of the route of administration.

First pass effect results in a very small portion of drug reaching the systemic circulation if it is swallowed. Sedation achieved with the DORMOSEDAN GEL is attributable to sublingual drug absorption. Peak concentrations occur approximately 1.83 hours after sublingual administration of DORMOSEDAN GEL. The peak concentrations observed after administration of DORMOSEDAN GEL are approximately 40% of those observed after intramuscular injection of detomidine solution. The absolute bioavailability of detomidine in DORMOSEDAN GEL is 22%.

EFFECTIVENESS:

A prospective, randomized, masked, multi-center study was conducted to evaluate under field conditions, whether DORMOSEDAN GEL provided sufficient sedation and restraint in horses to successfully conduct procedures requiring administration of a sedative. Two hundred and seventy client-owned horses of any breed or sex were sedated to facilitate grooming (including cleaning of the prepuce), hoof care, floating teeth (manually), passage of a nasogastric tube or endoscope, or radiography. Horses were enrolled in the study if they were a yearling or older, in satisfactory body condition, and had a history of requiring sedation or other means of strong restraint to enable similar procedures to be carried out. Horses were randomly assigned to receive DORMOSEDAN GEL sublingually at 0.040 mg/kg or placebo gel. After administration of treatment, each horse's level of sedation, degree of ataxia, heart rate and rhythm, and respiratory rate were assessed and measured to recovery. After an appropriate period of time elapsed to allow sedation to develop, a study veterinarian assessed and scored the ability to attempt and to complete the veterinary or husbandry procedure.

One hundred and twenty-nine DORMOSEDAN GEL-treated and 42 placebo-treated horses were included in the statistical analysis of effectiveness. Ninety-nine horses were excluded from the analysis due to failure to meet inclusion criteria or due to major protocol deviations. The veterinary or husbandry procedure was successfully completed for 98 of 129 DORMOSEDAN GEL-treated horses (76%) but only 3 of 42 placebo-treated horses (7%) (Table 3). The difference between the two treatments was statistically significant (p=0.0005).

Table 3: Treatment success rates (number of horses) by treatment group

Ability to perform the procedure score*	DORMOSEDAN GEL N = 129	Placebo N = 42
0	16	38
1	15	1
2	44	2
3	54	1
Success (score 2 or 3)	98	3

* 0: Poor – Strong resistance. 1: Fair. Moderate resistance. 2: Good. Some resistance, but the procedure could be performed. 3: Excellent. Procedure could be easily performed with insignificant resistance.

The following success rates with DORMOSEDAN GEL were recorded for electric clipping of hair (48%), cleaning the prepuce (81%), manual floating of teeth (89%), hoof trimming or shoeing (86%), passage of a nasogastric tube or endoscope (80%), or radiography (74%). At 40 minutes post dosing, 94% of DORMOSEDAN GEL-treated horses showed minimal, moderate or marked sedation compared with 14% of the horses treated with placebo. All DORMOSEDAN GEL-treated horses had recovered from sedation by 240 minutes post treatment.

DORMOSEDAN GEL was correctly administered sublingually (beneath the tongue) in 97% of horses with mild or no objection.

ANIMAL SAFETY:

In a multiple dose target animal safety study, DORMOSEDAN GEL was administered on three consecutive days to 6 horses per treatment group at 0, 1, 3 and 5 times the recommended label dose of 0.040 mg/kg.

The recommended dose (1X) induced sedation. Head droop caused transient edema of the head area, nasal/ocular discharge and congestion of oral mucous membranes. Ataxia, sweating and reversible penile prolapse were observed. Erythematous mucous membranes were seen at the area of dose application in 2/6 horses. Transient reductions were seen in heart rate, respiratory rate, and gut motility. Electrocardiography revealed increased incidences of vagally mediated arrhythmias (sinus arrhythmia, sinus block, 1st and 2nd degree atrioventricular block) as well as atrial or ventricular premature beats in the majority of horses. No clinical abnormalities were associated with the transient arrhythmias. Excessive or erratic urination were seen in isolated cases.

Similar treatment related findings were seen in horses receiving 3X and 5X doses. In most cases the incidence, severity and duration of the findings were dose dependent. All findings in all dose groups were representative of the alpha$_2$-adrenoreceptor drugs used in horses.

STORAGE INFORMATION:

Store at controlled room temperature 20–25°C (68–77°F), with excursions permitted to 15–30°C (59–86°F), in the original package.

HOW SUPPLIED:

3.0 mL graduated oral dosing syringe, 7.6 mg/mL detomidine hydrochloride.

U.S. Patent Nos.

DORMOSEDAN GEL® is a registered trademark of Orion Corporation..

TAKE TIME OBSERVE LABEL DIRECTIONS

Mfd by:

Orion Corporation
Turku, Finland

Dist by:

Pfizer Animal Health
Div. of Pfizer Inc
New York, NY 10017

12817US-1 DOR12019

Made in Finland
Date: December 2, 2009

CLIENT INFORMATION SHEET FOR OWNER/HANDLER USE AND SAFETY

This summary contains important information about DORMOSEDAN GEL. You should read this information before you administer DORMOSEDAN GEL to your horse. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about DORMOSEDAN GEL.

What is DORMOSEDAN GEL?

DORMOSEDAN GEL is an oromucosal sedative containing detomidine hydrochloride. It is prescribed by veterinarians to allow procedures to be done in an anxious horse. DORMOSEDAN GEL has not been shown to provide analgesia and should not be used for painful procedures.

How should the product be handled?

Always wear impermeable gloves when handling the dosing syringe with detomidine hydrochloride gel. Ask the veterinarian whether the gloves you plan to use are impermeable. For a minimum of 2 hours after administration, wear impermeable gloves when performing any tasks that require contact with the horse's mouth.

If you have or have had a history of cardiovascular disease (for example, hypertension or heart attack) take special precautions and avoid direct exposure to the dosing syringe. Do not come in contact with the mouth or any saliva of any horse that was treated with detomidine gel for a minimum of 2 hours.

What if I get the gel in my eyes or mouth?

Detomidine hydrochloride can be absorbed into your body after direct exposure through the eyes or mouth, and may cause irritation to these areas. In case of accidental eye exposure, flush with water for 15 minutes. If detomidine is exposed to the mucous membranes of the mouth, rinse without swallowing. In all cases of accidental exposure and possible ingestion, seek medical attention immediately. Accidental exposure could result in the drug affecting you, causing symptoms that include sleepiness, low blood pressure and slower heart rate. DO NOT DRIVE, because detomidine may cause you to feel drowsy or sleepy. Share the package information with your physician and tell the physician that the product contains an alpha$_2$-adrenoceptor agonist.

What if I get the gel on my skin?

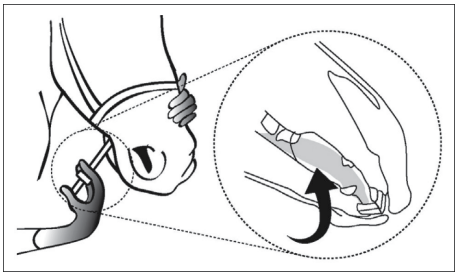
Detomidine hydrochloride can be absorbed into your body after direct exposure through the skin. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Contact your physician if you have any questions or concerns.

The material safety data sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in humans or horses or to obtain an MSDS for this product call 1-800-366-5288.

How is DORMOSEDAN GEL administered?

DORMOSEDAN GEL should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of gel you should give to your horse. The appropriate dose is delivered beneath the tongue (sublingually) and is not meant to be swallowed. Make sure there is no food in the horse's mouth prior to administration.

The following drawing demonstrates correct administration of DORMOSEDAN GEL beneath the tongue.



Following appropriate dosing of the gel, your horse should be kept in a quiet area until sedation is achieved.

If after 40 minutes there is inadequate sedation and you suspect that the horse swallowed or spit out some of the gel, contact your prescribing veterinarian. Do not repeat the dose.

If you believe the correct dose of detomidine gel was administered but the horse remains inadequately sedated, contact the prescribing veterinarian. Do not repeat the dose.

Contact your prescribing veterinarian immediately if the dosing syringe fails during the administration of detomidine gel and you are unsure if too much or too little of the dose was given.

Do not re-use partial dosing syringes. Any unused product or waste material should be disposed of in accordance with local requirements and Federal prescription drug disposal guidelines. Ask your veterinarian for this information.

What should I expect after administering DORMOSEDAN GEL?

Following appropriate dosing of the gel, your horse should be kept in a quiet area. As the drug takes effect, you will typically see the head lower and the front legs plant in a firm stance. This will usually take about 40 minutes. You may also notice slight swaying, sweating, salivation and slight muscle tremors. Be careful when handling sedated horses. Handling or any other sudden stimuli, including noise, may cause a defense reaction (for example, kicking) even in a horse that appears to be fully sedated. It may take up to 3–4 hours for the horse to recover from sedation. Withhold food and water until the horse has recovered.

What else should I know about DORMOSEDAN GEL?

As with all prescribed medicines, DORMOSEDAN GEL should only be given to the horse for which it was prescribed. This sheet provides a summary of information about DORMOSEDAN GEL. If you have any questions or concerns about DORMOSEDAN GEL or its effects on your horse or yourself, talk to your veterinarian.

EXCEDE®
(Ceftiofur Crystalline Free Acid)
Sterile Suspension

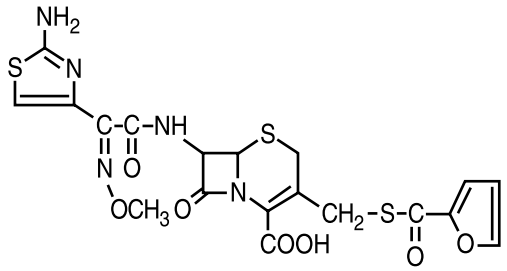
For intramuscular injection in the horse.

CAUTION
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
EXCEDE Sterile Suspension is a ready-to-use formulation that contains the crystalline free acid of ceftiofur, which is a broad spectrum cephalosporin antibiotic active against Gram-positive and Gram-negative bacteria including ß-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal, *in vitro*, resulting from inhibition of cell wall synthesis.

Each mL of this ready-to-use sterile suspension contains ceftiofur crystalline free acid equivalent to 200 mg ceftiofur, in a caprylic/capric triglyceride (Miglyol®) and cottonseed oil based suspension.

Figure 1. Structure of ceftiofur crystalline free acid:



Chemical name of ceftiofur crystalline free acid:
7-[[2-(2-Amino-4-thiazolyl)-2-(methoxyimino)acetyl]amino]- 3-[[(2-furanylcarbonyl)thio]methyl]-8-oxo-5-thia-1- azabicyclo[4.2.0]oct-2-ene 2-carboxylic acid

INDICATION
EXCEDE Sterile Suspension is indicated for the treatment of lower respiratory tract infections in horses caused by susceptible strains of *Streptococcus equi* ssp. *zooepidemicus*.

DOSAGE AND ADMINISTRATION
Shake well before using.

Administer two intramuscular injections to horses, 4 days apart, at a dose of 3.0 mg/lb (6.6 mg/kg). A maximum of 20 mL per injection site may be administered. Therapeutic drug concentrations are maintained for 6 days after the second injection (or a total of 10 days from the beginning of treatment) against *Streptococcus equi* ssp. *zooepidemicus.*

Table 1. Dosing Schedule for EXCEDE Sterile Suspension

Weight (lb)	Dose Volume (mL)
100	1.5
200	3.0
300	4.5
400	6.0
500	7.5
600	9.0
700	10.5
800	12.0
900	13.5
1000	15.0

Weight (lb)	Dose Volume (mL)
1100	16.5
1200	18.0
1300	19.5
1400	21.0
1500	22.5
1600	24.0
1700	25.5
1800	27.0
1900	28.5
2000	30.0

CONTRAINDICATIONS
EXCEDE Sterile Suspension is contraindicated in horses with known allergy to ceftiofur or to ß-lactam (penicillins and cephalosporins) group antimicrobials. Due to the extended exposure in horses, based on the drug's pharmacokinetic properties, adverse reactions may require prolonged care.

WARNINGS
Not for use in humans. For use in animals only. Keep this and all drugs out of reach of children. Consult a physician in case of accidental human exposure.

Do not use in horses intended for human consumption.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposure to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing protective gloves. Persons with a known sensitivity to penicillin or cephalosporins should avoid exposure to this product. In the case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g. skin rash, hives, difficult breathing) seek medical attention.

PRECAUTIONS
Prescribing antibacterial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the treated animal and may increase the risk of development of drug-resistant animal pathogens.

The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that can be fatal. If acute diarrhea is observed, additional doses of EXCEDE should not be administered and appropriate therapy should be initiated.

Due to the extended exposure in horses, based on the drug's pharmacokinetic properties, adverse reactions may require prolonged care. EXCEDE is slowly eliminated from the body, with approximately 17 days needed to eliminate 97% of the dose from the body. Animals experiencing adverse reactions may need to be monitored for this duration of time.

The use of ceftiofur has not been evaluated in horses less than 4 months of age and in breeding, pregnant, or lactating horses. The long term effects on injection sites have not been evaluated.

ADVERSE REACTIONS
The injection of EXCEDE Sterile Suspension in the horse may cause firmness, swelling, sensitivity, and/or edema at the injection site (see **ANIMAL SAFETY**).

A total of 373 horses of various breeds, ranging in age from 4 months to 20 years, were included in the field study safety analysis. Adverse reactions reported in horses treated with EXCEDE and the placebo control are summarized in Table 2.

Injection site swelling (edema) was reported in 10 of 278 (3.6%) EXCEDE-treated horses and 1 of 95 (1%) of the placebo-treated horses. Of the 10 EXCEDE-treated horses with injection site swelling, 8 horses had swellings of 4 cm or less in diameter, one horse had a 10 cm diameter swelling and one horse had injection site reactions to both injections measuring 25 x 12 cm each. The injection site reactions in EXCEDE-treated horses resolved over 1 to 20 days.

At least one episode of diarrhea, loose, soft, or cowpie stools were observed in 25 of 278 (9%) of the EXCEDE-treated horses and 7 of 95 (7%) of the placebo-treated horses. The duration of episodes in EXCEDE-treated horses ranged from a single observation of loose stool to observations lasting 6 days. All cases were self-limiting and resolved with minimal (a single dose of loperamide) or no treatment.

Table 2. Number of Horses with Adverse Reactions During the Field Study with EXCEDE

Adverse Reaction	EXCEDE (n=278)	Placebo (n=95)
Diarrhea/Soft Stool	25 (9%)	7 (7%)
Injection Site Swelling	10 (4%)	1 (1%)

The material safety data sheet (MSDS) contains more detailed occupational safety information. To obtain a material safety data sheet, please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

CLINICAL PHARMACOLOGY
Ceftiofur is a beta-lactam antibiotic from the cephalosporin class. Beta lactams exert their inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins, which are essential for synthesis of the bacterial wall. Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder) or ceftiofur crystalline free acid (EXCEDE Sterile Suspension) is rapidly metabolized to desfuroylceftiofur, the primary metabolite with antimicrobial activity. Two intramuscular injections of EXCEDE Sterile Suspension at a dose of 6.6 mg/kg body weight in the horse provide concentrations of ceftiofur and desfuroylceftiofur related metabolites in plasma above the therapeutic target of 0.2 µg/mL for the entire 96 hour (4 day) dosing interval and for 6 days after the second injection (or a total of 10 days from the beginning of treatment) (see Figure 2 and Table 3).

Figure 2. Average plasma concentration of ceftiofur and desfuroylceftiofur related metabolites in horses following the intramuscular administration of either EXCEDE Sterile Suspension at a dose of 3.0 mg/lb (6.6 mg/kg) administered twice at a 96 hour interval or NAXCEL Sterile Powder at a dose of 1.0 mg/lb (2.2 mg/kg BW) once daily for 10 consecutive days.

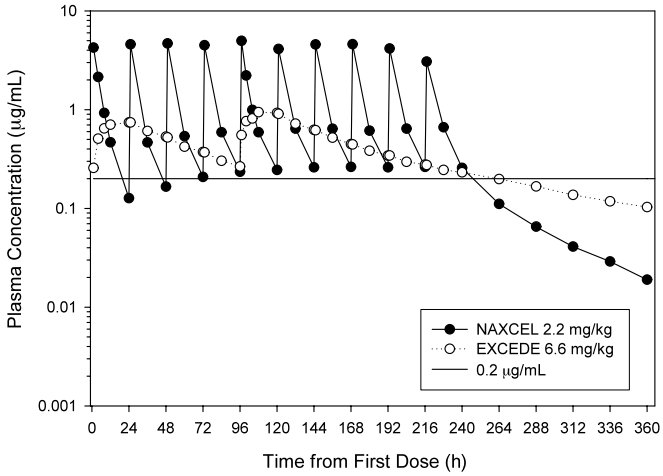


Table 3. Pharmacokinetic parameters measured after either two intramuscular injections of EXCEDE Sterile Suspension at a dose of 3.0 mg/lb (6.6 mg/kg) BW at a 96 hour interval or NAXCEL Sterile Powder at a dose of 1.0 mg/lb (2.2 mg/kg) BW once daily for 10 consecutive days are summarized in the following table.

PK Parameter	CCFA-SS at 6.6 mg/kg BW administered twice 96 h apart (Mean ± SD; n=12)		Ceftiofur sodium at 2.2 mg/kg BW once daily for 10 days (Mean ± SD; n=11)	
$AUC_{0-\infty}$ (μg•h/mL)	157 (19.1)		353 (44.9)	
$t_{>0.2}$ (h)	262 (29.0)		ND	
	Dose 1	**Dose 2**	**Dose 1**	**Dose 10**
T_{max} (h)	21.6 (5.8)	15.6 (6.3)	1.0	2.0 (3.3)
C_{max} (μg/mL)	0.78 (0.19)	1.0 (0.24)	4.31 ± 0.78	3.99 (1.23)

MICROBIOLOGY

Ceftiofur is a cephalosporin antibiotic. Like other ß-lactam antimicrobials, ceftiofur exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial wall. Ceftiofur is not active against *Pseudomonas* spp. and enterococci.

The minimum inhibitory concentration (MIC) values for ceftiofur against label-claim pathogens isolated from lower respiratory tract infections in horses enrolled in a 2007-2008 field effectiveness study are presented in Table 4. All MICs were determined in accordance with the *Clinical and Laboratory Standards Institute* (CLSI) standards.

Table 4. Activity of EXCEDE Against Pathogens Isolated from Horses Treated With EXCEDE in Field Studies in the U.S. During 2007-2008

Disease	Pathogen	Treatment Outcome	# of Isolates	Time of Sample Collection	MIC_{50} μg/mL	MIC_{90} μg/mL	MIC Range μg/mL
Lower Respiratory Tract Infection	*Streptococcus equi* ssp. *zooepidemicus*	Success	93*	Pre-Treatment	0.06	0.12	0.03-0.5
		Failure	42	Pre-Treatment	0.06	0.25	0.03-0.5

* One horse cultured *Staphylococcus aureus* (successfully treated) and is not represented in the table.

EFFECTIVENESS

A double masked, randomized, negative control, field study evaluated the effectiveness of two intramuscular doses of 6.6 mg/kg EXCEDE Sterile Suspension administered 4 days apart for the treatment of lower respiratory infections caused by *Streptococcus equi* ssp. *zooepidemicus* in the horse. In this study, a total of 278 horses were treated with EXCEDE, and 95 horses were treated with saline injections. One hundred ninety-three horses (136 EXCEDE and 57 saline placebo) were included in the statistical analysis. Therapeutic success was characterized by no worsening of clinical signs at Day 4, clinical improvement at Day 9, resolution of the clinical signs by Day 15, and no recurrence of clinical signs by Day 25 after initial dosing. EXCEDE was superior to the saline control. Table 5 summarizes the clinical success rates obtained 15 and 25 days after the first dose.

Table 5. Clinical success rates at Day 15 and 25

Effectiveness parameter	EXCEDE	Saline Control	P-value
Clinical success Day 15	73.53%	38.60%	N/A
Clinical success Day 25	69.12%	31.58%	0.0215

ANIMAL SAFETY

Two studies, a target animal safety (TAS) study and a pharmacokinetic (PK) study (see **CLINICAL PHARMACOLOGY** section), were conducted to assess the safety of EXCEDE in the horse.

In the TAS study, healthy adult horses received 6 intramuscular (lateral neck) injections of EXCEDE Sterile Suspension at doses of either 3.0 (1X), 6.0 (2X) or 9.0 (3X) mg/lb with a 4 day interval between each injection. In the TAS study, there were no treatment related gastrointestinal findings for the three EXCEDE Sterile Suspension treatment groups. In the PK study, one horse treated with 6.0 mg/lb (2X) EXCEDE experienced a mild episode of colic the day after the second injection of EXCEDE. The horse recovered without treatment.

Injection sites were observed in both studies. In both studies, the largest injection volume administered was 20 mL per injection site. There were no observations of erythema, necrosis or drainage at the injection sites in these studies. Firmness, swelling, and/or sensitivity were observed in at least one injection site in all horses treated at the label dose. In the TAS study, injection site reaction measurements ranged from no measurable reaction to 16 x 33 x 1.5 cm. In the PK study, the largest area of edema associated with the injection site ranged from no detectable reaction to a 30 x 36 cm area of edema. Injection site reactions developed within 2 days of injection and resolved within 1-18 days. In the PK study, 2 horses had small areas of firmness that had not resolved at the end of the study (21 days after injection).In both studies, a greater incidence of injection site reactions occurred after the second injection, and in several horses, swelling at the injection site resolved then recurred 1-5 days later.

In the PK study, several horses developed clinical signs consistent with foot pain (stiff in the front limbs when turned in tight circles, and increased pulses and heat to the front feet). One horse in the NAXCEL group and one horse in the 6.0 mg/lb (2X) EXCEDE group were euthanized due to laminitis. Clinical signs of foot pain (stiff front limbs and increased heat and pulses in feet) affected more horses, for a longer period of time, in all EXCEDE-treated groups as compared to the NAXCEL-treated group. The study housing (multi-horse pens on concrete slabs) and diet (free choice alfalfa/grass mix and once a day pellets) may have contributed to the development of foot pain. The prevalence and severity of injection site reactions in EXCEDE-treated horses may also have contributed to the development of a stiff gait. A causal relationship between ceftiofur and foot pain could not be definitively determined.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F). Shake well before using. Contents should be used within 12 weeks after the first dose is removed.

HOW SUPPLIED

EXCEDE Sterile Suspension is available in the following package size:
100 mL vial

U.S. Patent No. 5,721,359 and other patents pending.

NADA #141-209, Approved by FDA

Pharmacia & Upjohn Company

Division of Pfizer Inc, NY, NY 10017

www.EXCEDE.com or call 1-866-387-2287

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